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# Targeting Cortical Representations in the Treatment of Chronic Pain: A Review

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**Abstract**

Recent neuroscientific evidence has confirmed the important role of cognitive and behavioral factors in the development and treatment of chronic pain. Neuropathic and musculoskeletal pain are associated with substantial reorganization of the primary somatosensory and motor cortices as well as regions such as the anterior cingulate cortex and insula. What is more, in patients with chronic low back pain and fibromyalgia, the amount of reorganizational change increases with chronicity; in phantom limb pain and other neuropathic pain syndromes, cortical reorganization correlates with the magnitude of pain. These findings have implications for both our understanding of chronic pain and its prevention and treatment. For example, central alterations may be viewed as pain memories that modulate the processing of both noxious and nonnoxious input to the somatosensory system and outputs of the motor and other response systems. The cortical plasticity that is clearly important in chronic pain states also offers potential targets for rehabilitation. The authors review the cortical changes that are associated with chronic pain and the therapeutic approaches that have been shown to normalize representational changes and decrease pain and discuss future directions to train the brain to reduce chronic pain.

**Keywords**

rehabilitation, motor imagery, sensory discrimination, cognitive-behavioral

## Introduction

The critical role of the brain in pain has been assumed for centuries,[1] but conceptual models that emphasize that role, for example the neuromatrix theory,[2] have been few. The changes that occur in the central nervous system (CNS) when pain persists have revealed an even more important role of the brain than expected. Indeed, when pain persists, reorganization in the brain may actually contribute to chronic pain.[3] This finding has already led to a range of new treatments, with varying strength of evidence, that target these changes and appear to offer promising results. This review will outline the current state of the art and future directions in training the brain to lessen chronic pain.

## The Brain Responds to the Perceived, Not the Actual Reality

Pain is a conscious experience. That is, pain cannot exist outside of consciousness. In contrast, but often erroneously considered analagous, nociception can exist outside of consciousness. In fact, nociception can occur without the brain—high-threshold peripheral afferents and their spinal projections can be activated in the absence of brain activity. Indeed, tactile perception, pain, and other bodily feelings can be thought of as outputs of the brain that are based on an informed interpretation of the information coming from one's body. An example from tactile perception is the so-called rabbit illusion, which occurs when 2 sites on the arm are stimulated in a certain way such that touch is felt at a location between the stimulation sites at which no stimulation actually occurred. Brain imaging data show that the representation site in the brain that is activated corresponds to the perceived not the actual location of stimulation.[4] Similarly, pain emerges from the brain according to the apparent danger to body tissues and the need for a concerted response from the individual, not according to activity in nociceptive fibers or the actual state of the tissues.[5] The multifactorial nature of pain has been reviewed.[6]

This differentiation between nociception and pain is often ignored, such that the terms are used synonymously in the lay[7] and in the scientific[8] literature. The implications and impact of erroneously equating nociception and pain become larger as pain persists, in part because the nervous

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system and brain undergo changes that make the link between pain and tissue damage even more tenuous.[6] The more tenuous this link, the more treatment must look beyond the potential tissue damage. Intuitively, this realization is made clear by common characteristics of persistent pain—it may be poorly or negatively related to activity, can spread, move location, swap sides or limbs, and "have a mind of its own." Persistent pain is often associated with a range of perceptual and regulatory dysfunctions.[9] Such disturbances are difficult to attribute to tissue injury. Changes in the brain not only provide a more likely explanation for these effects, but they offer new targets for treatment of persistent pain.

## The Brain Changes When Pain Persists

Persistent pain is associated with sensitization of the neural network that subserves pain and disinhibition of surrounding or related neural networks. Sensitization is consistent with the fundamental property of biological systems to adapt according to use and biological advantage. That such adaptation occurs in neural systems is well understood—learning is one example—the principle of practice makes perfect and conditioning paradigms that have been a mainstay of psychological experiments for decades exploit this fundamental property at a cortical level (although the physiological adaptations that are involved are clearly not confined to the brain). Central sensitization is another example of adaptation.[10] The clinical manifestation of central sensitization, allodynia, and hyperalgesia occur with repeated activation of spinal nociceptors and offer biological advantage by increasing sensitivity to peripheral inputs. Increased sensitivity optimizes the likelihood of tissue healing and minimizes the risk of secondary injury. However, over time, sensitization may lose its adaptive value and become a problem of its own, such as in chronic pain.

Sensitization occurs in the spinal cord and supraspinal centers. In people with chronic pain, seeing a painful limb being touched can evoke pain and swelling even when the limb is not actually touched.[11] Imagined movements of a chronically painful limb can increase pain and swelling in the absence of detectable muscle activity or limb movement.[12] Imagined movements can also exacerbate phantom limb pain after spinal cord injury,[13] where exacerbation of peripheral or spinal nociceptive input is less likely.[14] These clinical observations demonstrate that sensitization is not confined to a single sensory modality. Rather, sensitization can extend to other modalities and triggers and can be enhanced by associative learning processes, so that pain is evoked through nonnociceptive channels.[15]

*Cortical disinhibition* refers to the loss or reduction of intracortical inhibition, which is critical for precise neural activations. The combination of sensitization and disinhibition drive systematic change in the response profile of neurons that represent the body. This type of change, called cortical reorganization, was first observed in the primary sensory and motor areas of animals following deafferentation.[16] A large amount of work has demonstrated reorganization in many cortical sensory and motor areas.[17] That a similar effect occurs in humans was illustrated when upper-limb amputees were stimulated on the lip.[18] The peak response to the stimulus, recorded over the contralateral primary sensory cortex, was shifted in the amputees. The cortical representation of the lip had invaded the area that normally represents the hand, which had since been amputated.[18] This shift was attributed to the loss of afferent input associated with amputation, but subsequent work, which compared cortical reorganization between amputees with and without phantom limb pain,[3] showed that this only occurred in those with phantom limb pain. Moreover, pain intensity strongly correlated with the magnitude of the shift of the lip representation. That is, cortical reorganization was not simply a result of amputation. Similar changes have also been observed in the anterior cingulate cortex and the insula,[19] The relation between pain and primary sensory cortex reorganization has since been observed in many chronic pain states, for example, upper-limb complex regional pain syndrome (CRPS),[20] carpal tunnel syndrome,[21] chronic back pain, and fibromyalgia.[22]

The primary motor cortex was first mapped in animals more than 100 years ago[23] and in humans 40 years later.[24] In contrast to the primary sensory cortex, which is organized spatially, thus holding maps of the internal and external surfaces of the body, the primary motor cortex is organized functionally.[25] The primary motor cortex does not hold a discreetly organized roster of body parts or movements, but rather, representations follow motor function and thus overlap one another, right down to the level of individual neurons.[26] Furthermore, motor maps are inherently variable: Movement-specific motor maps shift over days,[27] and stimulation of the same cortical motor neurons can evoke different movements even within recording sessions.[28]

Motor disinhibition has been observed in patients with chronic neuropathic pain[29] and migraine[30] and in CRPS.[20] Moreover, general cortical disinhibition going beyond the primary sensory and motor areas has been reported in people with phantom limb pain[31] and in people with chronic musculoskeletal pain.[22] In amputees with phantom limb pain, but not in those without phantom limb pain, lip movements invade the hand movement area in the motor cortex, and the magnitude of the shift is again related to pain.[32]

Some of these changes can occur quickly and have been observed in the prechronic stages, which suggests that this disinhibition may not only be a consequence but also a vulnerability factor for chronic pain. For example, experimentally induced pain can rapidly decrease motor cortex excitability, and simply seeing someone else being injured reduces motor cortex excitability in a site-specific manner,

as measured by muscle activity at the site being injured in the other person.[33] Higher-order body maps have also been examined in people with chronic pain. For example, the maps the brain uses for movement—the so-called working body schema—cannot be elucidated by relatively simple stimulus–response brain imaging paradigms. As a surrogate measure, timed motor imagery tasks are used. One such task is the left/right judgment task. According to an extensive body of work on this task,[34] judging whether a pictured hand or foot belongs to the left or to the right involves 3 sequential processes. First, we make an initial spontaneous judgment. This process is dependent on the deployment of attention to either side of the body, or to either limb, and the processing speed of the CNS. Second, we mentally move our own matching limb to mimic the posture of the limb shown in the picture. This requires an intact working body schema and its integration with premotor processes. Third, we confirm or deny the initial judgment. This is dependent on CNS processing speed. If the mental movement does not confirm the initial judgment, the process starts again,[34] which incurs a delay. The 2 primary outcomes of left/right judgments are reaction time and accuracy. Longer reaction times for pictures of 1 limb relative to the other probably reflect a bias in information processing away from the delayed side or toward the opposite side.[35] Reduced accuracy of left/right judgments probably reflects disruption of the cortical proprioceptive representation (or working body schema) of the limb.[36] Increased reaction times for pictures that correspond to the affected limb have been shown in people with CRPS[37] and in people with phantom limb pain after amputation or brachial plexus avulsion injury.[36,38] Decreased accuracy has been shown in people with phantom limb pain.[36]

Cortical reorganization in people with persistent pain is not limited to sensory and motor representations. Rather, there is evidence that the range of pathological or generalized pain syndromes such as CRPS, fibromyalgia, chronic pelvic pain, chronic back pain, and whiplash-associated disorders demonstrate disruption across efferent systems. For example, perceptual and autonomic disturbances are particularly common in CRPS.[39] Efferent system disruption in neuropathic and pathological pain states has been reviewed fully.[9]

## Harnessing Brain Plasticity to Treat People in Pain

The changes that occur in the brain when pain persists clearly present barriers to successful recovery. However, the plasticity that underpins them suggests that they may be responsive to targeted treatments. Such treatments can be grouped under cognitive-behavioral, sensory, and motor strategies.

### *Cognitive and Behavioral Strategies*

That pain emerges according to the apparent danger to body tissues and the need for concerted action, not according to the true danger or damage at a tissue level, means that anything that is detectable or accessible to the brain and relevant to the evaluation of danger to body tissue has the capacity to modulate pain. Many of the influences on pain may be implicit and involve nonassociative and associative learning processes, such as Pavlovian and operant conditioning, and can occur[40] entirely outside the awareness of the person.[15,41]

Patients who show high levels of pain behaviors and are very incapacitated by their pain appear to benefit from operant-behavioral treatment. The goals are to decrease pain behaviors; increase healthy behaviors related to work, leisure time, and the family; reduce medication; and change the responses of significant others from solicitous to distracting or ignoring. The majority of data concerning behavioral strategies show clear improvements in functional capacity, but positive effects on pain have also been reported in a range of chronic pain states.[42,43]

The cognitive-behavioral model of chronic pain emphasizes the role of cognitive and affective factors as well as behavior in the development and maintenance of chronic pain.[44] The core objectives of cognitive-behavioral treatment for chronic pain are to reduce feelings of helplessness and uncontrollability, establish a sense of control over pain, and instate behaviors that limit the impact of pain on quality of life. These objectives are achieved by the modification of pain-eliciting and -maintaining behaviors, cognitions, and emotions. The cognitive-behavioral approach teaches patients various techniques to effectively deal with episodes of pain. Pain-related cognition is changed by cognitive restructuring and pain coping strategies, such as diversion of attention, use of imagery or relaxation that increase self-efficacy, and cognitive reappraisal. The behavioral component incorporates increased activity, pacing, and activity planning. Several studies have demonstrated the efficacy of cognitive-behavioral pain management.[45] Another component of the cognitive-behavioral approach is education about pain and the factors that modulate it. Psychoeducation alone can lead to positive shifts in pain-related knowledge, catastrophizing, and participation in subsequent cognitive-behavioral or multimodal rehabilitation.[46-48]

Treatments that focus on the extinction of pain behaviors and the acquisition of healthy behaviors can alter brain processes related to pain. In anxiety disorders, it has been shown that exposure with or without additional pharmacological intervention can further alter brain processes related to stimuli that are relevant for the disorder.[49] The partial NMDA (N-methyl d-aspartate) receptor agonist d-cycloserine has been found to be effective in enhancing extinction of aversive memories and has been used as an effective adjunct

to exposure treatment. In addition, cannabinoids have been identified as important modulators of extinction[50] and might be interesting compounds for extinction training. Extinction is context specific, so training as many varied behaviors as possible, in many different environments, and the use of stress and pain episodes to train relapse prevention are important parts of this approach.[51]

## Strategies to Normalize Sensory Representations

Training sensory representations requires the delivery of stimuli to the body part of interest. Stimulation alone is seldom sufficient to modify sensory representations. Instead, the combination of the stimulus and its salience or functional context appears to be important. For example, although we stimulate the sole of the foot several thousand times a day simply by walking, the acuity of somatosensory receptive fields associated with the foot is low because the tactile stimuli from the foot are seldom salient. In contrast, tactile input from the hand is often salient or functionally important, which is reflected in the precision of tactile receptive fields associated with the hand. Stimulation of a body part is most likely then to induce changes in sensory cortical representation if the characteristics of the stimuli are important for activities such as playing a musical instrument or reading Braille or the objective of the task is important as, for example, in unwrapping food.[52]

Application of this principle to treating pain was first tested on upper-limb amputees with phantom limb pain[53] on the basis of somatosensory cortical reorganization in these patients.[3] Participants were required to discriminate between electrical stimuli of different frequencies, which were applied to 8 different locations on the stump of the amputated limb.[53] They were trained to discriminate the location or the frequency and received feedback on the correct responses. Treatment consisted of 90-minute training sessions, 10 in all, undertaken on consecutive days. The control group received an equal amount of attention. There were several outcomes that, together, strongly support the prediction that training somatosensory acuity would reduce phantom limb pain via an effect on cortical organization. First, performance and tactile acuity improved. Second, phantom limb pain was reduced by more than 60%. Third, cortical reorganization was reversed, such that the lip representation reverted to its normal location. Critically, the improvements in discriminative ability, pain, and cortical reorganization were strongly correlated. This result provides theoretical support for the idea that disrupted cortical representation actually contributes to the maintenance of chronic pain.[54]

The sensory discrimination training that was used successfully in people with phantom limb pain has since been adapted for clinical use.[55,56] In a pragmatic trial of tactile discrimination training, patients with CRPS of 1 arm discriminated between 2 stimuli of different widths (a pen lid and a wine cork) presented at 5 locations on their affected limb. Twice-daily tactile discrimination training for 10 consecutive days imparted significant reductions in pain and disability.[57] It is important to note that stimulation alone imparted no effect. That is, increased tactile acuity, decreased pain, and decreased disability were only induced when the patient was required to differentiate between stimuli during training. As would be predicted by the principle of functional salience, it seems to be the discrimination of distinct stimuli, rather than the stimuli per se, that imparts the effect.

Functional magnetic resonance imaging was used to investigate the effects of prosthesis use on phantom limb pain and cortical reorganization.[32] A myoelectric prosthesis provides sensory and visual as well as motor feedback to the brain. Amputees who used a myoelectric prosthesis reported less phantom limb pain and showed less cortical reorganization than patients who used either a cosmetic or no prosthesis at all. Activation of the cortical representation of the now absent limb via visual, tactile, and proprioceptive input seems to be important in decreasing phantom limb pain. It seems possible that preventing cortical reorganization might reduce the likelihood of developing phantom limb pain in the acute stage. One would predict that fitting and training with a myoelectric prosthesis early after amputation might have symptomatic as well as functional advantages.

## Strategies to Normalize Motor Representations

An important report that a mirror image of an amputee's intact arm induced the feeling in the amputee that the phantom limb had "come alive" and eliminated phantom limb pain[58] sparked a great deal of interest in the use of mirror therapy and virtual limbs for the treatment of neuropathic pain. Clinical trials of mirror therapy offer conflicting results.[59] Although a recent study for CRPS after stroke reported very large effects,[60] whether or not mirror movements are superior to motor imagery for neuropathic pain is yet to be clearly settled.[59] There is, however, good evidence that a graded motor imagery program, incorporating mirror therapy, is effective for CRPS and phantom limb pain after amputation or brachial plexus avulsion injury.[38,61-64] Graded motor imagery consists of 3 stages through which the patient progresses according to performance or on a time-contingent basis. The first stage involves hourly sessions of left/right limb judgments, which can be performed using online software (http://recognise.noigroup.com/recognise/). The second stage uses imagined movements, and the third stage involves mirror therapy, after which functional exposure and physical upgrading is undertaken. That the order of components appears to be important for the effect[63] is probably explained by cortical adaptation.

Another theory that has received a great deal of attention as it relates to mirror therapy is that of sensory-motor incongruence. The idea is that mirror therapy, graded motor imagery, and tactile training might correct cortical body maps, so as to remove the incongruence between motor commands and sensory feedback.[65] This notion was implied informally by Ramachandran et al[58] and posits that pain in the absence of ongoing tissue damage is caused by incongruence between motor intention and proprioceptive feedback. McCabe et al[66] examined the hypothesis in healthy volunteers who moved both arms up and down in a scissor-like manner. Placing a mirror between the arms meant that the seen movement of the arms was congruent but the motor command and proprioceptive feedback were not. The authors reported the presence of painful and nonpainful paresthesias as a consequence of the incongruent movement condition. Whether or not participants actually hurt during that experiment is questionable (the ratings on a 0- to 11-point numerical rating scale were all less than 2), and a subsequent attempt to induce pain via sensory-motor incongruence was unsuccessful.[67] However, it remains possible that in a sensitized or disrupted neurological system such as in neuropathic pain, sensory-motor incongruence might contribute to, or maintain, pain.

## Future Directions

It seems reasonable to suggest that sensory discrimination training and graded motor imagery might have a role in other chronic pain disorders for which changes in sensory representation, sensory acuity, or motor imagery performance have been identified. For example, sensory representation is disrupted[22] and tactile acuity is reduced[68] in people with back pain.

Motor imagery has recently been adapted for people with pain related to cauda equina injury. The approach, called virtual walking, involved paraplegic patients sitting in front of a screen projected onto which was a film of someone walking.[69,70] By placing a mirror over the upper body of the person in the film, the patient could be positioned to get a view of a full body walking toward them. Patients could move their upper body in time with the lower body in the film to get the experience that they were in fact watching themselves walk.[69] Although initial data appear promising, further work is clearly indicated.

Other brain-mediated disorders associated with chronic pain syndromes raise opportunities for novel brain-targeting treatments. For example, people with chronic CRPS often perceive that their affected limb is bigger than it really is.[71] Remarkably, viewing the limb through a magnifying lens increases the pain evoked by movements, and viewing it through minimizing lens decreases the pain evoked by movements.[72] Such studies raise the possibility that we might be able to manipulate these higher-order cognitive processes for therapeutic gain. Virtual reality training might be especially helpful in these cases.[73]

Finally, direct alteration of brain activation by brain stimulation or neurofeedback may be useful interventions in their own right or as adjuncts to behavioral treatments.[74,75] As noted above, extinction training and pharmacological interventions that modulate plasticity and enhance extinction might also be useful.

## Conclusion

A large body of evidence shows that chronic pain is associated with disruption of a range of body-related cortical representations. There is some evidence that this disruption contributes to, or maintains, chronic pain. The theory that the disruption reflects maladaptive neuroplastic changes underpins treatments that aim to normalize cortical representations as a way of treating chronic pain. Treatments that target sensory and cognitive representations using sensory and motor strategies show clear functional and symptomatic benefits. Future research should aim to unravel the complex relationships that almost certainly exist between disrupted representation of multiple efferent systems and chronic neuropathic and nonneuropathic pains. Finally, our understanding of the mechanisms by which disrupted cortical representations might contribute to or maintain chronic pain is incomplete. Longitudinal and controlled outcome studies are required.

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